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Aus der Oto-laryngologischen Klinik der Universität Basel
(Direktor: Prof. Dr. E. Lüscher)

Considerations of the Suspected Etiologic Factors Involved in Upper Respiratory Malignancies

Inaugural-Dissertation
zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt von
Paul J. Davis
von Buffalo, New York, USA

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Considerations of the Suspected Etiologic Factors Involved in Upper Respiratory Malignancies

The amount of carcinogenic agents uncovered to date numbers well upwards of 1000. Common among these are: coal tar derivatives, petroleum by-products, shale oil, arsenic, paraffin, anthracene, creosote, aromatic amines, benzene, chromates, β-naphthylamine, aniline dyes, ultraviolet rays, x-rays, radium, and fissionable materials. The purpose of this paper is to illustrate the close association between some of these acknowledged carcinogens and their possible causal influence on upper respiratory malignancies, i.e. in the nose, nasal sinuses, oral cavity, tongue, tonsils, epipharynx, mesopharynx, hypopharynx, and larynx.

Methodology of the Study

One hundred and thirty-six histologically confirmed upper respiratory malignancies treated between 1951 and 1957 in Professor E. Lüscher's E.N.T. Clinic of the University of Basel were the subject matter for this study. These patients were for the most part inhabitants of an industrial community. The use of a matched control population was purposely avoided so that background variables such as age, sex, dietary factors, and chronic infections would not be sacrificed. Among the points covered in a typical interview with each patient were: a detailed account of each patient's smoking and drinking habits, family history, age, patient's previous history as to endocrine disturbances, childhood diseases, infectious diseases (past or present, chronic or acute), metabolic diseases, G.U. disorders, weight fluctuations, dietary habits, accident history, diseases and trauma to the mouth, nose, throat, larynx, bronchi, and lungs, frequency of fluoroscope and x-ray examinations or treatments and, finally, details as to the patient's working or home environmental conditions with respect to humidity and temperature changes, air pollution by dust or fumes, and contact with chemical substances such as asbestos, silicates, nickel, arsenic, chromates, pesticides, coal tar products, petroleum products, exhaust gases, corrosive vapors, carcinogenic hydrocarbons, macromolecular compounds in the form of plastics, and organic and inorganic dyes including aniline.

To provide a finer evaluation of the material, the 136 cases in the combined study group were broken down into 6 anatomical subgroups: cancer of the larynx involved 44 cases; cancer of the tonsil, epipharynx, and mesopharynx, 23 cases; cancer of the hypopharynx, 23 cases; cancer of the nose and nasal sinuses, 18 cases; cancer of the oral cavity and tongue, 16 cases; and sarcomas at all sites amounted to 12 cases.

The total number of cases in this study is not as large as is in some papers, but we are confident that smaller statistics are also of importance, particularly when approached from a qualitative viewpoint.

Of the 136 cases, 68% (92 patients) were exposed to established chemical carcinogenic agents, 3.7% (5 patients) were exposed to established physical carcinogenic agents, 84% (113 patients) consumed alcohol in varying quantities, and 86% (113 patients) were smokers.

There were only 4 patients who had no known exposure to either chemical or physical carcinogens, alcohol or tobacco. Upon comparison of these 4 patients with the remaining 132 patients in the combined study group, it is interesting to note that all are female, none had larynx cancer (n.b. all the 44 patients in the larynx cancer group had association with some known carcinogenic agent, alcohol, or tobacco), and only one of the 4 had a typical simple squamous cell carcinoma, that is, the kind of carcinoma displayed by the majority (91%) of the combined study group. Two of the remaining 3 had undifferentiated squamous cell carcinomas and one had a sarcoma.

In attempting to determine which of the environmental etiological carcinogens seemed to be most significant, it was found that only 3.7% of the combined study group (5 patients) had known exposure to physical carcinogens, 3 having received excessive Roentgen irradiation and 2 with traumatic experiences.

Those with known exposures to chemical carcinogens comprised 68% of the combined study group (91 patients). The percentages of the prominent chemical carcinogenic agents found in this study are as follows: 59% coal tar derivatives, 53% metallic dusts (Si, Ni, Zn, Cr), 22% aniline dyes, 18% arsenic, 16% exhaust fumes, 16% carcinogenic hydrocarbons, 9% corrosive vapors, and 4% asbestos dust.

Two further statistical relationships pertaining to chemical carcinogenic exposures are: (1) The percentage of patients in each group that was affected by some chemical agent. (2) The percentage of the chemical carcinogens affecting each group.

Table I

Group Relationships to Chemical Carcinogens

Group	(1) % of group affected by chemical carcinogens	(2) % of chemical carcinogens that affected the group
Larynx	70%	34%
Tonsil-Epipharynx-Mesopharynx	70%	18%
Hypopharynx	61%	15%
Nose-Nasal Sinuses	44%	9%
Oral Cavity-Tongue	81%	14%
Sarcomas at all sites	75%	10%

Alcohol and tobacco also seemed to be implicated in the etiology of upper respiratory malignancies.

Those who claimed to be drinkers comprised 84% (113 patients) of the combined study group. In reality, 21% were what we considered heavy

drinkers, i.e. those who consistantly drank at least one liter of wine per day (or its beer equivalent), plus a minimum of at least five shots. Of the total 113 drinkers, 107 were males. Further, of the 6 female drinkers, none were categorized as heavy drinkers.

A percentage comparison of heavy drinkers in the 6 anatomical subgroups revealed that the entire hypopharynx population consisted of heavy drinkers, i.e. 52% of the total of heavy drinkers. Twenty-six per cent of the tonsil-epipharynx-mesopharynx group, 18% of the larynx group, and 8% of the oral cavity-tongue group were heavy drinkers. No heavy drinkers were found in the nose-nasal sinus group or in the sarcoma group.

A further statistical breakdown showed that 86% (117 patients) were smokers. Of the 117 smokers, 116 were males. Only one female smoked, and her consumption was considered very light, amounting to an average not exceeding 3 cigarettes daily.

The quantative degree of the smoking habit was calculated in terms of cigarette units, i.e. one pipe load being equivalent to two and a half cigarette units, one stumpen (a medium sized cigar without a tip) being equivalent to 4 cigarette units, and one cigar equaling 5 cigarette units. As is conventionally practised, one is considered a light smoker with a consumption of 1 to 9 cigarette units per day, a medium smoker consumes 10 to 19 cigarette units per day, and one in the heavy smoker category smokes from 20 to 34 cigarette units per day. Those who smoked more than 35 cigarette units a day were considered in an excessively heavy group.

Among the 117 smokers, the percentages of smokers in the combined study group as well as for each individual group is given in Table II.

Table II

Smoking Analysis within each of the Groups

	Combined Study Group	Larynx	Tonsil Epipharynx Mesopharynx	Hypopharynx	Nose-nasal Sinuses	Oral cavity–Tongue	Sarcomas of all Sites
Light (1–9)	7%	5%	16%	0%	8%	0%	25%
Moderate (10–19)	21%	17%	16%	18%	50%	20%	25%
Heavy (20–34)	39%	41%	42%	59%	17%	40%	0%
Excessively Heavy (over 35)	33%	37%	26%	23%	25%	40%	50%

Statements have been made by some investigators that larynx cancer is associated more closely with cigar and pipe smoking than with cigarette smoking. Our investigation has shown that cigarette smoking is in no way a minor factor in the development of laryngeal cancer as evidenced by the fact that 54% of the smokers in the larynx group smoked cigarettes, whereas, in comparison, only 46% smoked cigars, stumpen, or pipes.

Three of the patients observed were tobacco chewers. One developed a nasal sinus sarcoma, another a squamous cell carcinoma of the tongue, and the third a squamous cell carcinoma of the left tonsil.

A survey was made to evaluate inhalation patterns of smokers and probable etiological relationships of inhalation to malignant formations. The inhalation patterns were so closely associated with what was smoked that no significant conclusions from the inhalation factor alone could be ascertained. With the exception of 3 patients, all those who smoked cigars, stumpen or pipes (total of 81) did not inhale. Among the 70 cigarette smokers, with the exception of 6, all did inhale.

Next, an endeavor was made to establish a correlation between tumor development in any of the 5 different anatomical regions within the upper respiratory area and a given occupational group. Within our 136 cases, we had representatives of the metal, fabric and textile, chemical, coal and tar, rubber and plastic industries; construction trades; clerks, farmers, carpenters, bakers, performers, and domestic workers. It was found that the distribution of patients in each occupational group showed no more than a random dispersement among the 5 anatomical subgroups. Only one occupational category suggested an increased tumor frequency within a given anatomical group. Reference here is made to 2 performers. They both exhibited a common denominator of vocal strain and both developed squamous cell carcinomas of the larynx. One drank moderately and smoked 25 cigarette units a day and the other was a non drinker who averaged only one cigarette a day. Neither had a known exposure to chemical carcinogenic agents. The most that could be said for vocal strain under the circumstances, therefore, is that it may suggest an etiological or contributory relationship in the development of laryngeal carcinoma, as already emphasized by *Clerf*[1].

The basic types of upper respiratory cancer, i.e. squamous cell carcinoma, adenocarcinoma, and undifferentiated squamous cell carcinoma, were investigated as to their sex distribution within the anatomical subgroups as shown in Table III.

Table III

Basic Types of Upper Respiratory Cancer and the Sex Distribution within the Anatomical Subgroups

	Combined Study Group		Larynx		Tonsil Epipharynx Mesopharynx		Hypopharynx		Nose-nasal Sinuses		Oral cavity–Tongue	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Total number of patients	109	15	42	2	18	5	22	1	12	6	15	1
Number with squamous cell carcinoma	102	11	40	2	18	3	22	1	7	4	15	1
Number with adenocarcinoma	4	0	0	0	0	0	0	0	4	0	0	0
Number with undifferentiated squamous cell carcinoma	3	4	2	0	0	2	0	0	1	2	0	0

Discussion

Sex Distribution

Carcinoma of the larynx has long been considered a man's disease. An early British report by *Semon* on 212 laryngeal cancer cases collected from 1878 to 1906 showed a ratio of 5:1. A similar ratio is seen in England today[6]. A series of 1498 laryngeal cancer patients presented by *Baltzell* and *Putney* show a sex ratio of nearly 13:1. The 1948 death rates in the United States reflect a ratio of 10:1[7]. The sex ratio in our combined study group reflecting all upper respiratory sites was 6:1 whereas the laryngeal site alone showed a ratio of 22:1 in favor of the male patients. An explanation for the fact that, in most instances, the male is more subject to the development of laryngeal cancer than the female is given by *Hesse*[8], who suggests hormonal influences. He expresses the possibility that, although the male hormone in itself is not the carcinogenic factor, it may play the role of a promoting factor ("Begünstigende Rolle") or that the female hormone may have an inhibiting character against the development of laryngeal carcinoma.

Hueper[3] in his comprehensive review of sex distribution states that the sex ratios are variable for different regions, population groups, and races, as well as for different periods and may even show under circumstances an inversed character. He therefore concludes that sex ratios evidently are not sex connected but exposure related.

Age Distribution

Although generalized cancers occur at any time, they usually fall into a pattern of distribution whereby the peak of incidence for women ranges from the ages of 45 to 54 and that for men comes a little later in life, between the ages of 55 and 65. Sarcomas, on the other hand, seem to display a somewhat random distribution, spreading themselves pretty evenly throughout life with a slightly lower incidence level between the ages of 1 and 16 than between 16 and 65. After 65, the incidence rate assumes a gradual decrease[9].

A comparison of our group of 124 upper respiratory carcinomas with the above described pattern for carcinomas at all sites revealed a parallel course. As for sarcomas, however, our small group showed an irregular shift from the usual random distribution. Of the 12 sarcoma patients, over 50% (7 patients) were above the age of 65. It will be interesting to see if larger studies of upper respiratory sarcomas display a similar result.

Dietary Factors

Although the interview included a detailed interrogation of present and former nutritional habits, the patients were unable to elicit sufficient information to allow any conclusions to be made regarding significant influences

which the diet may exercise on the development of tumors. It can be stated that none of the patients examined were troubled with dietary or vitamin deficiencies.

Chronic Infections

All the patients were questioned concerning infections in detail but with special emphasis on their general resistance to infections and if they were troubled with upper respiratory or general chronic infections, tuberculosis, or syphilis. Our statistical results could show no positive evidence of an association between chronic infections and tumor development and were in agreement with those of *Wynder*, *Bross*, and *Day*[7], as well as *Blümlein*[10], whose recent studies were unable to show any evidence that tuberculosis or syphilis play any part in the production of laryngeal cancer.

X-Ray

The literature attesting radiation therapy as a responsible agent for the development of malignant tumors in the neck region is most impressive[11–15]. In most of the cases presented by these authors, an average latent period of 16 to 32 years was evidenced between the irradiation treatment for a benign process and the development of the malignant neoplasm. *King*, *Cole*, *Horwitz*, and *Klopp*[16] made an interesting report of a case of laryngeal carcinoma appearing in a patient treated 11 months previously by a thyroid ablation dose of I^{131} for a cystadenocarcinoma of the thyroid. In view of the short latent period one can discuss whether the intense irradiation to the larynx, the adjacent carcinogenic structures, or a combination of both was responsible for the subsequent carcinoma of the larynx.

Supporting experimental evidence for irradiation being the cause of neoplasms was shown by *Koletsky* and *Guftafson*[17]. They demonstrated the carcinogenic potency of whole body radiation, not just in the skin and subcutaneous tissue, but also in the viscera, and hypothesized that in addition to direct tissue injury, an indirect or systemic mechanism induced by radiation may have been operative in promoting carcinogenesis.

The first patient in our records to receive radiation treatment was subjected to seven successive fluoroscopings 12 years before his malignancy developed. He was occupationally in contact with metallic dusts and tar products and was a light smoker and a moderate drinker. The other two patients however were non-drinkers, non-smokers and were both housewives with no known exposure to carcinogenic agents. X-ray treatments for tuberculosis of the cervical lymph nodes were instituted 34 years in one patient and 36 years in the second prior to the development of the malignant neoplasm. Corresponding to the findings of other authors, our cases also displayed long latent periods between the exposure to irradiation and the development of the malignancy.

Trauma

There has been very little supporting evidence in the literature for upper respiratory malignant growths being the result of trauma. One case was reported by *Hoshiya*[18] of a primary epiglottis cancer that developed three years after swallowing a fish bone which was first removed from the larynx several months after it was swallowed. Although some authors claim that a single traumatic experience has no causal influence on the development of cancer (*Berenblum*[19], *Waser*[20], *Linell*[21]), *Fritzsche*[22] recognizes such a relationship, but only with the condition that a pre-neoplastic condition precedes the traumatic experience.

The one case we should like to mention is that of a galvanizer who had, to the best of our knowledge, no known pre-neoplastic condition before his accident. At that time, he fell head first into a bath of dilute hydrochloric acid and nearly suffocated. The traumatic experience, in our opinion, cannot be considered the exclusive cause of the meristoma of the epipharynx and mesopharynx which developed 20 years later in view of his constant contact with metallic dusts throughout this entire period. The trauma, however, might be considered a promoting or contributing factor in the subsequent development of the patient's sarcoma.

Alcohol

Wynder, Bross, and *Day*[7], in their study of the effect of alcohol in laryngeal cancer, found a significantly higher percentage of heavy drinkers in their population with cancer than in a matched control population free of cancer. In a well planned study to disentangle the effect of smoking on alcohol consumption by studying the differences in alcohol consumption within groups of men with similar smoking habits, *Wynder* et al. were able to show that there was no association between this disease and the drinking of wine, beer, or moderate quantities of spirits, but that the consumption of 7 or more shots of spirits a day might increase the risk of the disease by some 5- or 10-fold.

Further documentation of the significance of alcohol on larynx carcinoma was made by *Barroilhet*[23] in a clinical survey of his patients with carcinoma of the larynx and by the Registrar-General of England and Wales[24] in addition to *Kennaway* and *Kennaway*[25, 26], who reported that innkeepers, barmen, and waiters showed a high mortality rate from larynx cancer.

A statistical survey showing the significance which alcohol consumption can play beyond mere coincidence was that by *Kennaway*[27] when he reported that bartenders have almost 25 times more cancer of the esophagus than clergymen.

To the experienced clinician, the hypopharynx cancer patient gives the most frequent impression of consuming a large amount of alcohol. We have seen that more than 20% of the drinkers in the combined study group were in the heavy drinking class. Over half of these heavy drinkers were patients

with carcinoma of the hypopharynx, and nearly the entire heavy drinking population remaining, 44%, were patients in the larynx and tonsil-epipharynx-mesopharynx groups. This should be suggestive that excessive alcohol consumption is a contributing factor to the development of cancer, especially in the region of the hypopharynx.

Tobacco

There is so much controversy at the present time as to the relationship of smoking to cancer that the information presented by the various investigators is becoming increasingly more difficult to evaluate. Most of the statistical studies and animal experiments have gone a long way towards furnishing us with valuable data necessary for the solution to this problem[5, 7, 23, 28–34].

A most noteworthy observation was made recently by *Cooper*, *Lindsey* and *Walker* in England and *Latarjet*, *Cusin*, *Hubert-Habart*, *Muel*, and *Royer* from the Institut du Radium, Fondation Curie, in Paris. Examining chemically[35] and by spectral analysis[36] the tar of cigarette smoke and cigarette paper for carcinogenic polycyclic hydrocarbons, they were able to substantiate Roffo's earlier experiments[37–40] by spectroscopic examination of tobacco tar, that 3:4 benzpyrene is present in the cigarette tobacco. 3:4 benzpyrene was also evidenced in the cigarette paper.

Animal experiments to evidence the carcinogenicity of tobacco tar were made by a number of investigators, among which were *Schurch* and *Winterstein*[41], *Roffo*[42], *Chikamatsu*[43], *Flory*[44], and *Wynder* and *Graham*[45]. The skin of mice or rabbits was painted with tobacco tar or condensations of tobacco smoke, and in all these experiments, success in producing papillomas and carcinomas in the experimental animals was attained.

A striking casuistic observation of smoking being an etiological factor in the development of cancer was that described by *Heermann*[46]. Identical twins were both of the same profession, master mechanics. One smoked heavily and developed a vocal cord carcinoma, while the other, who did not smoke, remained healthy in spite of the same inherited characteristics.

The number of smokers was found to be quite high in our study population. Upon close inspection of the smoking statistics, however, it is seen that the effect of smoking was not equal throughout the entire upper respiratory tract. Considering just the heavy and excessively heavy smokers in the nose-nasal sinus group and in the sarcoma group, one finds the percentage of smokers to be 50% and lower. In the other groups it is between 68% and 82% (Table II). The standard deviation between the combined study group (with 72% being heavy and excessively heavy smokers) and the individual groups amounted to 10.5 allowing a normal distribution ranging from 51% to 93%. All of the individual groups fall into this normal range of distribution with the exceptions of the nose-nasal sinus group (42%) and the sarcoma group (50%).

Therefore, it would be appropriate to claim smoking as an etiological factor in the upper respiratory tract malignancies, but more so for cancers

in the larynx, tonsil, pharynx, oral cavity and tongue regions than for cancers in the nose-nasal sinus regions or for sarcomas.

Inasmuch as 116 of the 117 smokers in the combined study group are men, we may contrast the percent of our cigar, stumpen, and pipe smoking population to *Gsell*'s study of male smoking habits in this area[47]. In a random population of a large local manufacturing firm studying 1795 male employees, *Gsell* found that only 19.2% of the smokers chose cigars, stumpen, and pipes. Those smokers in our combined study group, all with upper respiratory malignancies, preferred to smoke cigars, stumpen, and pipes to the extent of 58%. Furthermore, nearly three quarters of the hypopharynx patients were in the cigar, stumpen, and pipe smoking group. Therefore, two conclusions might be advanced.

1. There seems to be a rather substantial correlation between this type of smoking and the overall incidence of upper respiratory malignancies.

2. The swallowing of cigar or pipe tobacco juice might have been the local carcinogenic factor which was responsible for the close association of cigar, stumpen, and pipe smoking to hypopharynx carcinoma.

The narrow correlation of cigar, stumpen, and pipe smoking to hypopharynx carcinoma was statistically verified by calculating the normal range of distribution for the cigar, stumpen, and pipe smokers within the individual groups as compared to this type of smoking as found in the combined study group. The normal distribution ranges from 38% to 62%. Cigar, stumpen, and pipe smoking in the hypopharynx group was 70% however (Table IV). This is not within the normal range of distribution and therefore indicates the significance of cigar, stumpen, and pipe smoking to hypopharynx cancer.

As it is known, when there are injuries to the mucous membranes of the physiologically narrow hypopharynx passage, for example by acids or caustics, a developing cancer usually appears at the site of the former lesion. Perhaps it is possible that minute lesions in the narrow hypopharynx passage could have existed prior to the continuous passage of tobacco juices and that this constant exposure to the carcinogenic fractions in the tobacco juices might have given rise to the malignant growth.

It must be stated, however, that tobacco consumption in general must *not* be indiscriminately overemphasized. Our statistics offer support to this thought by virtue of the fact that of the 19 female cases in the combined study group, 18 were not smokers. They must have been subjected therefore to some other cancer causing influence.

Occupational Carcinogens

There has developed a rapidly growing increase in the awareness and appreciation of the dangerous attributes of our new artificial industrial environment prompted by the rapid increase in factual information on occupational and environmental carcinogenic agents during recent decades. Contributors to the wealth of information depicting the importance of industrial carcinogens have been names like *Kennaway*[2], *Heuper*[3], *Macdonald*[4], and *Blümlein*[10], to mention but a few.

Reports on individual carcinogens at all sites similar to those mentioned in this investigation for carcinogens affecting the upper respiratory tract have been made, for example, by *Neubauer*[48], as well as *Dérobert* and *Hadengue*[49], who described arsenic dusts as probable carcinogenic irritants. *Stewart*[50], in his speech to the New York Academy of Medicine, mentioned two dyes, Light Green S.F. and Brilliant Green F.C.F., that have caused subcutaneous sarcomas in the rat. Further study may link these and similar dyes with the carcinomas and sarcomas of textile workers observed in our combined study group who, otherwise, have no known exposure to chemical carcinogens. Some of our patients working as spinners in the silk industry, as well as mechanics and machinists in other local industries, have had their carcinogenic exposure partially explained by *Huguenin* and co-workers[51]. They suggest that the respiratory tract can be subjected to carcinogenic agents through the inhalation of finely dispersed mineral oil mist or fumes from high-speed machinery, from quenching baths in foundries, from high-pressure grease guns and diesel jets, from spraying parts with oil and from high temperature operations. Studies on the carcinogenic constituents of shale oil and related aspects were published by *Berenblum* and *Schoental*[52, 53]. Possible connection between the origin of cancer and silicates was described by *Krejci*[54], while *Cadotsch*[55] reported a similar possible connection for acid vapors (chromic, sulphuric, and prussic), as well as silver, nickel, and chromium dusts.

That occupational exposure to one of the known carcinogenic agents over a long period of time might be considered an etiological factor for upper respiratory malignancies was the original motivation for making this statistical survey. It was found that coal tar and metallic dusts seem to be the most persistent agents. The question of whether there is any predominant localization for the carcinoma theoretically caused by these agents can only be answered by citing the relatively high number of laryngeal cancers that are associated with metallic dusts.

Just by grouping the patients occupationally without asking in detail what their real chemical exposures are is insufficient. In general, less attention should be placed on the occupational group relationships to cancer and more efforts should be directed towards uncovering the possible carcinogenic agents a person may come in contact with in his environment or at his job, that each job must be evaluated in terms of the carcinogenic exposures it presents. A fitting example of this is the difference in attitudes one would exhibit when evaluating one of our laryngeal carcinoma patients. A glance at his occupation as a customs officer would hardly arouse any interest in a carcinogenic-minded observer. But there certainly would be a much different response on the part of this observer if he were to realize the fact that this patient had been a customs officer for freight, particularly that which supplies the local chemical industry, and that he was in continuous contact with asbestos, arsenics, aniline dyes, coal tar products and their derivatives, as well as corrosive vapors.

Judging a whole industry for the incidence of cancer which it presents can be instructive, especially with large scale surveys, but in the final anal-

ysis, a presentation of specific carcinogenic agents and the most likely forms of human contact for these agents seems to be a most constructive approach.

Syncarcinogenesis (Co-carcinogenesis)

Based on our material and what has been found in the literature, it can be said that in the etiology of upper respiratory cancer, occupational exposure to carcinogenic agents on one side, and heavy to excessive smoking and alcohol consumption on the other, play important roles (Table IV).

Table IV

Occupational Chemical Carcinogens, Alcohol and Smoking as Factors Involved in the Development of Malignancies in this Study

	Combined Study Group	Larynx	Tonsil Epipharynx Mesopharynx	Hypopharynx	Nose-nasal Sinuses	Oral cavity–Tongue
Occupational chemical exposures	68%	70%	70%	61%	44%	81%
Alcohol consumption, heavy only	21%	18%	26%	52%	0%	8%
Smokers of cigarettes only	36%	50%	35%	26%	28%	37%
Smokers of cigars, stumpen & pipes only	50%	43%	48%	70%	39%	56%
Heavy and excessive smokers combined	62%	73%	56%	78%	28%	75%

As far as the localization of the cancer within the upper respiratory area is concerned, the nose-nasal sinus group shows no convincing evidence of association with tobacco or alcohol (see Tables II and IV). Further, with respect to localizations, chewing and/or the smoking of cigars, stumpen, and pipes, as well as excessive alcohol consumption are predominant in the hypopharynx region. In all the other groups, an approximately equal distribution of these three factors is found. This evidence combined seems to support *Bauer*'s theory of syncarcinogenesis[9], whereby one factor alone need not be identified as the sole causative factor for the development of cancer. The actual growth of the tumor, according to Bauer, is the end phase of a step by step development, in which specific and nonspecific stimuli work together. *Butenandt*[56] adds that when a critical value is attained, the threshold for the malignancy is exceeded and the malignant growth takes its course. In such a concept, one may assume that the various stimuli can be in the form of chemical and physical carcinogens, tobacco, alcohol, chronic infections, viral influences, as has long been stressed by Oberling[57, 58], and also genetically inherited individual responsiveness or susceptibility[4].

We must presume that, according to this theory, there are many causes and that measures must be taken to minimize one's exposure to the known carcinogens. The alcohol exposure is one which must be controlled by the individual. Although smoking could also be individually controlled, an alternative was proposed by *Wynder* of a more effective tar filter which would bring most of a heavy smoker's tar intake down to the equivalent of a light to moderate smoker. With respect to the chemical and physical carcinogenic exposures, the important task of primary prevention does not belong to the medical domain but is reserved to the chemist, physicist, and engineer. It is up to these members of the team to devise safe production and handling procedures, and, when necessary, to develop non-carcinogenic substitutes[59].

Summary

One hundred thirty-six patients with histologically confirmed upper respiratory malignancies were reviewed with respect to the etiological factors involved in their carcinomas and sarcomas. Occupational chemical exposures as well as abuse of alcohol and tobacco were the principle offending etiological factors. The possibility of x-ray and trauma as carcinogenic factors was also discussed. The multiplicity of exposures in many cases offered support to the syncarcinogenic (co-carcinogenic) theory for the transformation from the non-pathological and/or benign stage into the malignant tumor growth. Of all the anatomical sites in the upper respiratory area, the hypopharynx was the most severely affected region of all from exposure to excessive drinking and cigar, stumpen and/or pipe smoking (as versus cigarette smoking). Furthermore, a much stronger correlation was found to exist for cigar, stumpen, and/or pipe smoking than for cigarette smoking in the development of upper respiratory tract malignancies, although the role played by cigarette smoking was by no means insignificant. Prophylactic measures for a stricter industrial control of chemical carcinogens was suggested as well as a more cautious approach to excessive drinking and smoking on the part of the individuals having these habits.

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